MEDICAL STAFF CONFERENCE

Lactic Acidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. BOUSHEY:* A 31-year-old Caucasian male was admitted to the Neurology Service because of weakness. Following trauma to the left ear at age 9, he noticed progressive deafness. At age 11 he was said to have an abnormal gait. At age 24 he first began wearing a hearing aid.

Since age 17 he has noted "dizzy spells" characterized by twitching of the left forearm but not associated with loss of consciousness. One year before admission to this hospital he had two fainting spells which could not be characterized further. In the past three years his weight had decreased 30 pounds and he had noticed progressive wasting and weakness in both the upper and the lower extremities. Also he reported having five soft bowel movements a day since visiting British Honduras 18 months before hospital admission.

At age 22 the patient began to have polydipsia and polyuria and was found to have diabetes mellitus. He was treated initially with regular insulin, but soon thereafter treatment was changed to phenformin, 50 mg three times a day, a treatment that was still being followed at the time of admission to hospital. His family history is strongly positive for diabetes: His father, maternal grandfather and two maternal aunts had maturity-onset diabetes.

Physical examination: Funduscopic examination revealed retinitis pigmentosa, arteriolar narrowing, waxy exudates, and numerous microaneurysms. Results of examination of the heart, chest, and abdomen were within normal limits. The testes were soft and small. Both plantar arches were noted to be high. Other abnormalities, confined to the neurologic system, included bilateral neurogenic hearing loss, weakness of both shoulder and hip girdle muscles, cerebellar signs with ataxia, and bilaterally hyperactive knee jerks with positive Babinski responses bilaterally.

Laboratory studies: Packed cell volume 35 percent, leukocytes 6,700 cells per cu mm, urine pH 6.0, 24-hour urine protein 2.6 grams. The urine was negative for ketone bodies. Serum sodium was 135, chloride 102, carbon dioxide 23, and potassium 5.4 mEq per liter. Serum creatinine was 1.6 mg per 100 ml, and creatinine clearance was calculated at 25 ml per minute. Total serum protein was 6.3 grams per 100 ml, cholesterol 326 mg per 100 ml, and uric acid 7.8 mg per 100 ml. Serum protein electrophoresis was within normal limits. A chest radiograph and an electrocardiogram were within normal limits.

Five days after admission the patient vomited three times and passed three soft-formed stools. He remained afebrile but became tachypneic and appeared dehydrated. At this time serum sodium was 140, chloride 100, potassium 6.7, and carbon dioxide 7.0 mEq per liter, yielding an anion gap of 33 mEq per liter. Blood glucose was 127 mg per 100 ml and serum acetone was negative. The packed cell volume had risen to 45 percent, and the leukocyte count was 13,200 with 80 percent

*Homer A. Boushey, Jr., M.D., Intern in Medicine.

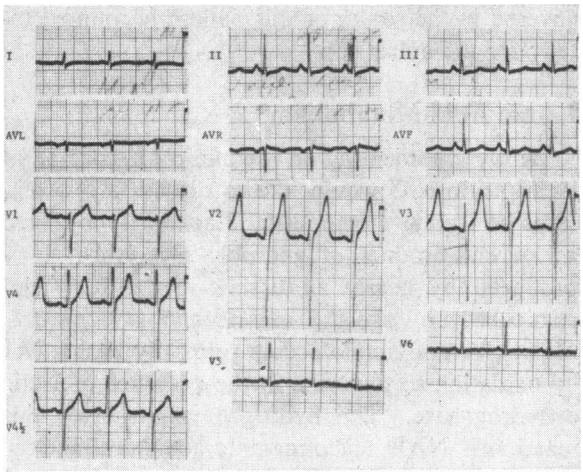

Figure 1. — Electrocardiogram showing peaking of T-waves in leads V_2-V_4.

polymorphonuclear forms. Six hours later the serum sodium was 140, chloride 98, potassium 7.8, and carbon dioxide 5.0 mEq per liter, yielding an anion gap of 37 mEq per liter. Arterial pH was 7.17. Blood glucose was 122 mg per 100 ml, and acetone was not present in the serum.

A repeat chest radiograph was within normal limits, but a repeat electrocardiogram (Figure 1) showed peaking of the T-waves in leads V_2 through V_4.

The total bicarbonate deficit was calculated at approximately 370 mEq, and treatment was initiated with intravenous dextrose and 0.5 normal saline solution with 90 mEq of sodium bicarbonate. After a total of 100 mEq of sodium bicarbonate was administered, serum sodium was 133, chloride 95, potassium 5.7, and carbon dioxide 5.0 mEq per liter. Serum acetone was still absent. After a total of 180 mEq of sodium bicarbonate, the serum potassium had fallen from 5.7 to 4.0 mEq per liter, and the carbon dioxide had risen from 5.0 to 10 mEq per liter. After 225 mEq of sodium bicarbonate, serum sodium was 133, chloride 100, potassium 4.0, and carbon dioxide 28 mEq per liter. Serum creatinine had risen to 1.9 mg per 100 ml, the blood urea nitrogen to 153 mg per 100 ml. The intravenous fluids were discontinued on the following morning and the patient felt well. Phenformin therapy was discontinued and insulin therapy begun. The serum lactic acid level during the acute episode was increased, confirming a diagnosis of lactic acidosis.

DR. SMITH:* Thank you very much, Dr. Boushey. The patient is here for presentation. I am afraid the factors of greatest interest to us today will not be revealed by physical examination. (Patient enters.) How are you feeling today?

PATIENT: I am feeling better, much better.

DR. SMITH: What was the main problem that was bothering you when you came to the hospital?

PATIENT: When I entered the hospital I had diarrhea. It started about a year ago.

DR. SMITH: Dr. Williams, do you have any points you would like to bring out on history?

DR. WILLIAMS:† I wanted you to tell us when the diarrhea improved.

PATIENT: A week ago.

DR. WILLIAMS: What happened at that time?

PATIENT: My medications were changed.

DR. WILLIAMS: Phenformin was stopped and insulin therapy begun at that time. His physical findings are not apparent at present. They are confined to the neurological examination and to the examination of the eye.

DR.WILLIAMS: Thank you for coming in. (Patient leaves.)

DR.SMITH: The discussion this morning will not be related to the patient's neurological deficit nor to his diabetes *per se,* but to the peculiar form of acidosis which was the most striking feature of his clinical course in the hospital. Dr. Williams has been particularly interested in this form of acidosis and has measured the levels of lactic acid in this patient. I would like to ask him to open the discussion.

DR. WILLIAMS: In summary, this patient is a 31-year-old male with a congenital neurologic disorder characterized by mental retardation, retinitis pigmentosa, deafness, cerebellar ataxia, and myopathy. He also has juvenile diabetes mellitus with onset at age 22 and has been treated for the last nine years with phenformin, 150 mg per day. After admission to the hospital and while apparently feeling quite well, he had sudden onset of severe acidosis with a significant anion gap. I would like to discuss two aspects of this patient's clinical problem: (1) the cause of the acidosis and (2) the relationship of this acidosis to the phenformin therapy.

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†Hibbard E. Williams, M.D., Associate Professor of Medicine.

TABLE 1.—*Acidosis with Anion Gap—Causes.*

Diabetic ketoacidosis
Uremic acidosis
Drug ingestions
Lactic acidosis

Acidosis with an Anion Gap

The causes of acidosis associated with an anion gap are shown in Table 1. The most important form of acidosis of this type is diabetic ketoacidosis. In this clinical situation the anion gap is related to the presence in the serum of increased amounts of ketone bodies, particularly β-hydroxybutyrate and acetoacetate. Although this patient did have diabetes mellitus, it is clear he did not have ketoacidosis. He did not have serum acetone measurable at any time during the episode of acidosis.

The second cause of this syndrome is uremic acidosis. This is another very common cause of acidosis associated with an anion gap. Patients with uremic acidosis have accumulation of sulfate and phosphate as well as certain organic acids in the serum, some known but some as yet unidentified. Lactic acid may be elevated in the serum of patients with uremic acidosis.

The third consideration is drug ingestion. Here I refer specifically to salicylate poisoning, where acidosis is seen commonly. The anion in this situation is lactate. Paraldehyde ingestion has been associated with acidosis, but the mechanism for the acidosis is not well understood. Methanol and ethanol in excessive amounts produce severe acidosis with accumulation of other anions. With ethanol ingestion this probably represents lactate as well as acetate. In methanol ingestion, formate is probably the more important anion. Finally, ethylene glycol ingestion has been associated with acidosis and an anion gap.

The fourth category, lactic acidosis, is exemplified by the problem seen in the patient presented today. This patient had abrupt onset of acidosis. At that time the serum level of lactate was measured at 17 micromoles per ml, which is approximately ten to fifteen times the normal level of 1 micromole per ml. (A pyruvate level was not estimated.) At the time this lactic acid level was drawn, the anion gap was estimated at approximately 35 mEq. With the addition of this lactate concentration to the sum of the chloride and the carbon dioxide concentrations, the anion gap returns to the normal range. Hence, that lactate recovered in the serum of this patient accounted totally for the anion gap.

Lactic Acid Metabolism

Before commenting on the clinical syndrome of lactic acidosis, I would like to discuss a few features of lactate metabolism. Lactate is produced as an end-product of anerobic glycolysis. It is produced by nearly all tissues in the body but particularly by skeletal muscle and erythrocytes. Metabolism of lactate occurs primarily in the liver by oxidation to pyruvate in the presence of lactic dehydrogenase. The hydrogen receptor for this reaction is NAD (nicotinamide adenine dinucleotide) which is reduced to NADH as oxidation of lactate occurs. Although this reaction is reversible, the equilibrium of the reaction strongly favors the reduced product lactate so that the normal lactate-pyruvate ratio is approximately 10:1 (that is, for one mole of pyruvate there are approximately ten moles of lactic acid). The subsequent metabolism of lactate is dependent upon the metabolism of pyruvate. There are two major pathways for pyruvate metabolism: (1) oxidative decarboxylation to acetyl coenzyme A in the Krebs cycle and (2) conversion to phosphoenolpyruvate on the gluconeogenic pathway to glucose. Regardless of the underlying defect, the accumulation of lactic acid in blood must result from one of two mechanisms: (1) increased production of lactate or (2) decreased utilization of lactate. Increased production is observed in situations associated with increased glycogenolysis, particularly muscular exercise, hyperventilation, and administration of glucagon, epinephrine, or fructose. Much less is known about the utilization of lactate. Decreased lactate utilization probably occurs whenever tissues are unable to oxidize lactate to pyruvate, to oxidize pyruvate sufficiently rapidly in the Krebs cycle, or to convert pyruvate to glucose by the gluconeogenic pathway.

The accumulation of lactate is always associated with the appearance of an equivalent number of hydrogen ions. Regardless of the arterial pH, in the subsequent discussion when I refer to lactic acidosis I imply lactate accumulation with or with-

TABLE 2.—*Lactic Acidosis—Classification.*

I. Primary
II. Secondary
A. To diseases associated with hypoxemia
B. Idiopathic

out acidosis, since the buffering ability of the blood may maintain arterial pH within the normal range despite the presence of increased amounts of lactate.

The Clinical Syndromes Associated With Lactic Acidosis

Table 2 outlines the classification of the lactic acidosis syndromes in man, based on Huckabee's classification.[1,2] Group I, the so-called primary type, refers to those situations in which the accumulation of lactate is in response to an overproduction of pyruvate with an appropriate amount of lactate being formed. Such situations include muscular exercise, hyperventilation, and administration of glucagon or epinephrine. In this group acidosis is usually not present and the lactate-pyruvate ratio is normal, 10:1.

Patients included in the category of Group II have lactic acidosis secondary to some underlying disease process. In Group IIA lactic acidosis is associated with those diseases in which hypoxemia plays a major role (acute hemorrhage, severe circulatory collapse, cyanotic congenital heart disease, and severe congestive heart failure). In these patients the serum lactic acid level is quite high, the lactate-pyruvate ratio is increased (implying accumulation of lactate in excess of that expected from the amount of pyruvate present), and acidosis may be quite severe.

Group IIB, referred to as idiopathic lactic acidosis, includes those patients who have sudden onset of lactic acidosis in the absence of an underlying disease process or precipitating event. The acidosis seen in the patient presented this morning is probably best classified as idiopathic lactic acidosis. He was feeling well in the hospital, he had no hypotension or hypoxemia, his appetite was good, and except for mild diarrhea he had no complaints. Suddenly one evening severe vomiting developed and the complete picture of lactic acidosis was documented. The onset of this syndrome was sudden without an obvious precipitating event.

Table 3 outlines some of the clinical characteristics and laboratory findings of spontaneous idiopathic lactic acidosis. Onset is rapid, often in a matter of hours as was the case with this patient. The specific clinical features include (1) changes in the state of consciousness and (2) signs of hyperventilation. Changes in the state of consciousness may vary from mild lethargy to stupor and eventually to coma. The mortality of the syndrome has been directly related to the degree of impairment in the state of consciousness. Hyperventilation, representing respiratory compensation for the severe metabolic acidosis, is identified by the presence of Kussmaul breathing. As has been pointed out by others,[3] hyperventilation *per se* may lead to lactate accumulation. The question of whether hyperventilation is secondary or primary has not been resolved in all patients. There is a very high mortality associated with this syndrome; in approximately 75 percent of the recorded cases the patients died. Death usually occurs rather soon after onset of the syndrome, usually in a matter of hours or days.

TABLE 3.—*Lactic Acidosis—Clinical Characteristics.*

Acute onset
Changes in state of consciousness
Hyperventilation
High mortality
Low serum bicarbonate and pH
Elevated serum potassium
Normal or low serum chloride
Anion gap
Elevated blood lactate and increased L/P ratio
Other abnormal findings

The laboratory features of the disease are characteristic. As one would expect, the serum bicarbonate level is low. In the recorded cases this has varied from 5 to 15 mEq per liter, usually closer to 5 than to 15. The serum pH is appropriately reduced and has varied from 6.98 to 7.25. The serum potassium is usually elevated in the range of 6 to 7 mEq per liter, representing a secondary response to the extracellular acidosis. The serum chloride is usually normal, although it may be somewhat depressed. The serum sodium is likewise usually normal. When the sum of the sodium and potassium cations exceeds the sum of the chloride and bicarbonate anions by greater than 15 mEq, an anion gap is said to exist. As the name of the syndrome implies, the blood lactate levels are elevated above the normal level of 1 micromole per ml. After muscular exercise one may see an increase in blood lactate levels to 4 or 5 micromoles per ml. In patients with spontaneous idiopathic lactic acidosis, however, the serum lactate level usually exceeds 7 micromoles per ml and may rise as high as 30 micromoles per ml (approximately 270 mg of lactate per 100 ml of blood). Coincidental with this increase in blood lactate is an increase in the lactate-pyruvate ratio, sometimes to as high as 60:1. Other abnormal findings include marked leucocytosis, an increase in the serum glutamic-oxaloacetic transaminase level perhaps related to changes in the liver blood flow, and an

TABLE 4.—*Lactic Acidosis—Associated Conditions.*

Chronic renal disease with uremia
Infection—septicemia
Diabetes mellitus
Pancreatitis
Cirrhosis
Pregnancy
Cardiovascular disease

increase in the level of serum phosphate as noted by Tranquada.[4,5]

Table 4 outlines the underlying diseases or associated pathological conditions which have been noted in patients with idiopathic lactic acidosis. These disorders are not thought to be a primary cause of lactic acidosis in patients in whom this syndrome has been reported. It is quite possible, however, that in the proper circumstances any one of these conditions could lead to lactic acidosis. The most common association is chronic renal disease with uremia. Actually in most patients the renal failure is fairly mild; most of the patients have only modestly lowered creatinine clearances. There have been only a few patients with severe uremia and associated uremic acidosis in addition to lactic acidosis. Infection has been a very common feature. This includes infection in the skin, in the lung, and particularly in the urinary tract. Acute pyelonephritis represents one of the more commonly associated conditions. Septicemia with Gram-negative organisms has been a problem in some of these patients.

Diabetes mellitus is also a frequent complication in patients with lactic acidosis. Both growth-onset and maturity-onset forms of diabetes have been described with lactic acidosis. The association of lactic acidosis with phenformin therapy is discussed below. Cirrhosis has been found in a small number of patients, and acute pancreatitis has been a problem in some. There appears to be an increased incidence of this syndrome in pregnancy, particularly in the third trimester and at the time of delivery. Finally, some patients have had severe cardiovascular disease, especially coronary artery disease and peripheral ischemic vascular disease. Although these are thought to be associated conditions, their role in the primary precipitation of lactic acidosis is not really defined.

Table 5 outlines in rather naive form the treatment of lactic acidosis. Obviously any hypoxia should be decreased, with use of oxygen and intermittent positive pressure breathing if necessary. It is important to maintain an adequate circulating blood volume, and hypovolemia must be treated actively. A central venous pressure catheter is particularly useful in evaluating adequacy of volume replacement. Although the maintenance of blood pressure is important, vasoconstrictive agents should be avoided since the effect of some of these agents on muscle blood flow may lead to a worsening of lactic acidosis due to relative hypoxemia of the skeletal muscles.

TABLE 5.—*Lactic Acidosis—Treatment.*

Decrease hypoxia
Correct dehydration and hypovolemia
Maintain blood pressure
Correct acidosis
Dialysis

The fourth point is obvious and important—namely, correction of the acidosis. It should be done quickly with large amounts of bicarbonate given intravenously. Often doses of bicarbonate greater than 200 to 400 mEq are necessary for complete correction of the acidosis.[6] The use of intravenous fluids containing lactate should be avoided in the treatment of this type of acidosis. It is important to monitor the serum potassium level during the treatment of the acidosis, as the serum potassium level tends to fall with abrupt alkalinization. Tranquada[7] suggested the use of methylene blue in these patients. Methylene blue is capable of oxidizing reduced NADH to NAD, thereby shifting the equilibrium of lactate toward pyruvate. Tranquada used this in a few patients with some apparent success, but it has not been evaluated on a large scale. Dialysis has been suggested and has been used in some patients, but it is difficult to explain its effectiveness, particularly since many dialysis fluids contain lactate. As noted, the prognosis for patients with this syndrome is poor; despite therapy, 75 percent of the patients reported in the literature have died.

Lactic Acidosis and Phenformin Therapy

What is the relationship of the lactic acidosis in this patient to the phenformin therapy? Figure 2

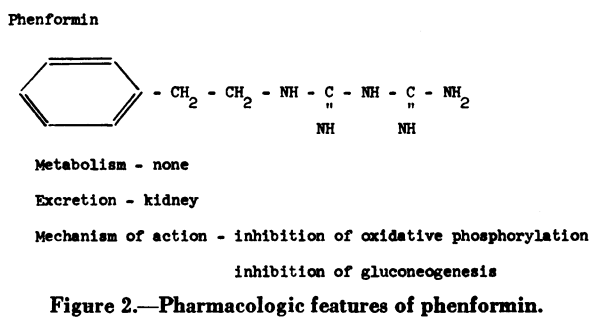

Figure 2.—Pharmacologic features of phenformin.

outlines some important pharmacologic features of phenformin. This oral hypoglycemic agent is one of the class of biguanide compounds known for some time to produce hypoglycemia. Note that it is not a sulfonylurea drug. It is absorbed well from the gastrointestinal tract. It is probably not metabolized in man; a single dose of phenformin will be excreted unchanged in the urine and feces in 24-48 hours. Excretion by the kidney is a very important feature which should be emphasized. The blood level of phenformin is very dependent upon the glomerular filtration rate and will increase remarkably in the presence of renal insufficiency. Speculations as to the mechanism of action of phenformin have been discussed for a number of years. Phenformin produces hypoglycemia only in diabetic patients; it is not effective in producing hypoglycemia in normal subjects.

Two major mechanisms of action have been proposed. Historically, inhibition of oxidative phosphorylation has been considered the major site of action. This has been demonstrated by *in vivo* and *in vitro* studies in experimental animals.[8] Presumably phenformin inhibition of NAD-dependent pyruvate oxidation, or the cytochrome oxidase system, leads to an increase in anerobic glycolysis and thereby to a secondary increase in glucose uptake in peripheral tissues such as muscle. Because rather large amounts of drug are necessary to inhibit oxidative phosphorylation in experimental studies, it has been questioned whether this mechanism is important in diabetic subjects receiving relatively modest doses of the drug. More recently a second mechanism of action has been emphasized —that of inhibition of gluconeogenesis.[9] *In vivo* and *in vitro* evidence of phenformin inhibition of gluconeogenesis from such substrates as lactate, pyruvate, alanine, and serine has been demonstrated. The exact site of inhibition of gluconeogenesis is unknown. An important feature of this mechanism is its demonstration at relatively low concentrations of drug—those obtainable in diabetic subjects receiving the usual recommended doses of phenformin. It seems likely that this is the more important mechanism of action of this drug in man.

The relationship of phenformin to lactic acidosis in diabetic subjects is not clear. Most of the diabetic patients in whom lactic acidosis has developed while they were taking phenformin had growth-onset diabetes. All of those reported have had some renal insufficiency, and in many it was quite severe. The onset of the lactic acidosis was sudden as it was in the patient presented today. It has been suspected for a number of years that phenformin was the precipitating agent in the acidosis. A problem exists in this explanation. As many physicians have pointed out, most diabetic patients treated with phenformin do not accumulate lactate, and secondly, spontaneous lactic acidosis occurs in diabetes mellitus without the use of phenformin. However, it is possible to speculate on the association of this syndrome with phenformin therapy in certain diabetic subjects. Since all diabetic patients reported with this syndrome have had renal insufficiency and since the excretion of phenformin is dependent on a normal glomerular filtration rate, it is likely that phenformin gradually accumulates in the blood of these patients until it reaches a level capable of inhibiting oxidative phosphorylation. Under these conditions lactate would accumulate, eventually resulting in the clinical picture of lactic acidosis.

I think this situation may have occurred in the patient presented today. He has some renal insufficiency as evidenced by a creatinine clearance of 25 ml per minute. Although he was treated with phenformin for a very long period, it is conceivable that the development of renal insufficiency, perhaps as a result of Kimmelstiel-Wilson disease, led to the gradual accumulation of phenformin in the blood and the precipitation of an episode of lactic acidosis.

In summary, I believe this patient represents an instance of spontaneous lactic acidosis in man—probably secondary to phenformin therapy. He responded well to bicarbonate therapy and removal of phenformin. Unfortunately, I am unable to speculate on the relationship of this metabolic disturbance to the underlying neurological disorder in this patient. Perhaps this latter problem will form the basis of another Grand Rounds exercise in the future.

DR. SMITH: Thank you very much, Dr. Williams. We have time for questions or comments. Dr. Michael Berry is an expert in this area and has had long interest in it.

DR. BERRY:* Perhaps I should congratulate the patient on his recovery rather than the physicians, because I really think the patient deserves most of the credit. You will note that after 180 mEq of

*Michael N. Berry, M.D., Associate Clinical Professor of Clinical Pathology and Laboratory Medicine.

bicarbonate were administered the serum bicarbonate rose from 5 to 10 mEq per liter. After a further 45 mEq the serum bicarbonate rose from 10 to 28 mEq per liter. My interpretation of these changes is that resumption of normal liver function led to an increased removal of lactate from the blood. If we assume that the lactate was distributed throughout all the cell water, the bicarbonate deficiency was about 1,000 mEq, not 300 mEq. As Dr. Williams emphasized, these patients really need intensive care. I think that often we do not realize the severity of the acidosis. Frequently very few clinical signs of acidemia are evident, and a virtually normal P_{CO_2} is found in the face of an arterial pH of approximately 7.0. This may be related to the insidious onset of the acidosis. The lactic acid may accumulate over a period of several days without the respiratory compensation generally associated with acute metabolic acidosis.

One word about the etiology of this syndrome. There is considerable evidence that the normal liver can remove lactic acid from blood at rates far in excess of the capacity of other tissues to form it.[10] It follows that prolonged accumulation of lactate in blood indicates a failure of hepatic function. This applies not only to lactic acidosis secondary to shock or to myocardial infarction where the splanchnic circulation is impaired, but also to those cases classified as idiopathic lactic acidosis, many of which have been associated with phenformin intoxication.

Recent work by Mulhausen and coworkers[11] has underlined this relationship. Nearly all of the 91 subjects with cirrhosis studied by these investigators had some degree of hyperlactatemia, and at least ten patients could be classified as having severe lactic acidosis. Thus, although only about 40 percent of patients with idiopathic lactic acidosis have overt liver disease, in the present state of our knowledge it would seem desirable to regard every patient with lactic acidosis as having some disturbance of hepatic function.

Editor's Follow-Up:

After the case had been presented at this conference, a renal biopsy was performed on the patient. Electron microscopic examination demonstrated features consistent with Kimmelstiel-Wilson disease. Because of the possibility that the patient might have Refsum's disease, a specimen of serum was examined for phytanic acid, but none was detected. Following discharge from the hospital he was treated with NPH insulin and diphenylhydantoin. Diabetic control was excellent, myoclonic jerking movements decreased, and his weight gradually increased.

REFERENCES

1. Huckabee, W. E.: Abnormal resting blood lactate: I. Significance of hyperlactatemia in hospitalized patients, Amer. J. Med., 30:833, 1961.

2. Huckabee, W. E.: Abnormal resting blood lactate: II. Lactic acidosis, Amer. J. Med., 30:840, 1961.

3. Zborowaka-Sluis, D. T., and Dossetor, J. B.: Hyperlactatemia of hyperventilation, J. Appl. Physiol., 22:746, 1967.

4. Tranquada, R. E.: Lactic acidosis: A review, Calif. Med., 101:450, 1964.

5. Tranquada, R. E., Grant, W. J., and Peterson, C. R.: Lactic acidosis, Arch. Int. Med., 117:192, 1966.

6. Waters, W. C. III, Hall, J. D., and Schwartz, W. B.: Spontaneous lactic acidosis: The nature of the acid-base disturbance and considerations in diagnosis and management, Amer. J. Med., 35:781, 1963.

7. Tranquada, R. E., Bernstein, S., and Grant, W. J.: Intravenous methylene blue in the therapy of lactic acidosis, Arch. Intern. Med., 114:13, 1964.

8. Davidoff, F.: Effects of guanidine derivatives on mitochondrial function. I. Phenethylbiguanide inhibition of respiration in mitochondria from guinea pig and rat tissues, J. Clin. Invest., 47:2331, 1968.

9. Patrick, S. J.: Effects of phenformin and hypoglycin on gluconeogenesis of rat tissue, Can. J. Biochem., 44:27, 1966.

10. Berry, M. D.: The liver and lactic acidosis, Proc. R. Soc. Med., 60:1260, 1967.

11. Mulhausen, R., Eichenholz, A., and Blumentals, A.: Acid-base disturbances in patients with cirrhosis of the liver, Medicine, 46:185, 1967.

PRESSURE-REGULATED VENTILATORS PROSCRIBED IN CARDIAC ARREST

"If you are using a ventilator [on a patient in cardiac arrest], you have to use a volume ventilator since the type that is pressure-regulated will be tripped every time you compress the chest, and the patient will end up getting zero ventilation. That's an extremely important point; you cannot use a pressure-sensitive ventilator to ventilate a patient on whom you are doing cardiac compression. It has to be a volume respirator."

—JAMES R. JUDE, M.D., Miami

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